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Electrochemical sensor without calibration

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(56) Related Art
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ABSTRACT

Electrochemical sensor, comprising a thin elongated insulating substrate (1) supporting two conductive strips (4, 5) of width L and L', whose facing edges (4a, 5a) are insulated from each other by a space (6) of width δ, a insulating covering film (2), comprising a connecting window (8) and at least one measurement window (11) provided with two openings (12, 13) separated by a portion (14) of said covering film (2), and delimiting the useful surfaces of measurement (16) and reference (17) electrodes, each opening (12, 13) having at any point dimensions measured perpendicularly to the median line (3) such that the furthest edge (12b, 13b) from the edge (4a, 5a) of the portion of the strip (4, 5) forming the electrode (17, 16) which said opening (12, 13) does not uncover is situated at a distance comprised between $L + \delta$ and δ (respectively $L' + \delta$ and δ) and the closest edge (12a, 13a) at a distance greater than δ.

Application to glucose sensors.

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COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

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Invention Title: **ELECTROCHEMICAL SENSOR WITHOUT CALIBRATION**

The following statement is a full description of this invention, including the best method of performing it known to us

ELECTROCHEMICAL SENSOR WITHOUT CALIBRATION

The present invention concerns an electrochemical sensor, intended to be disposable for measuring the concentration of a constituent in a sample of a solution, a fluid or an effluent by means of a portable electronic measuring apparatus, without it being necessary to implement beforehand calibrating means which depend upon the manufacturing batch of said sensor.

The invention concerns more particularly a sensor of this type used for the ambulatory medical follow-up treatment of a patient, requiring the measurement of the concentration of a constituent in a biological body fluid, such as the blood sugar level of a person suffering from diabetes.

Over the past ten years, disposable electrochemical sensors intended to be used for biological measurements have undergone considerable development. Generally, they are formed by an insulating support of small dimensions, supporting at least two electrodes which are electrically separated and able to be connected to a measuring apparatus, the measuring electrode being also coated with a specific reactant of the constituent whose concentration one wishes to measure. The measurement is effected by depositing the sample to be analysed onto a zone marked by an opening made in a covering film allowing the electrodes and portions of the insulating substrate to appear. Such measurement is effected indirectly by the exploitation of an electric signal generated by the interaction between the reactant and the constituent whose concentration one wishes to measure. Amongst other parameters, the intensity of this signal depends upon the surface of the electrodes.

Such exploitation of the electric signal generally consists of conductometric, voltammetric, conductimetric, coulometric or polarographic measurements allowing the electronic measuring apparatus to be calibrated as a

function of the intensity of the received electric signal so as to display directly on a display device the concentration of the constituent according to a determined mode (mg/dl, mmol/l). In order for the displayed value really to correspond to the concentration present in the sample, the interaction between the constituent and the reactant should be effected rigorously in the same way, i.e. the electric signal produced should be identical whichever sensor is used. In order for such sensors to be disposable, they must be inexpensive, and for this reason they can only be mass produced in batches. However much care is taken over the manufacture of such sensors, as regards both the construction and the dosage of the different components of the sensor, small variations from one batch to another are inevitably observed, such variations being prejudicial to the reliability of said sensors.

In other words, a specific calibration curve able to be selected from the specific calibration curves stored in a memory of the measuring apparatus corresponds to each manufactured batch. For this purpose, the packaging of sensors presently on the market comprises, either a code number which has to be introduced into the apparatus by means of a digital keyboard, or calibrating means which have to be put in place in the apparatus before the first measurement. The calibrating or data inputting means may be formed by a test-sensor having calibrated resistance, a small bar provided with a bar code able to be read by the apparatus, or by an electronic chip.

In addition to the fact that the risk of error cannot be ruled out, for example by omitting to perform to a new calibration when one starts on a packaging containing sensors from a different batch to the preceding one, the calibrating means which are currently necessary substantially increase the cost of each sensor, i.e. eventually the cost of a medical treatment effected under monitoring of measurements effected by a sensor, for

example with a glucose sensor for persons suffering from diabetes.

An object of the present invention is to overcome the drawbacks of the prior art by providing a mass produced sensor, but not necessitating the use of calibrating means, whatever the manufacturing batch from which said sensor comes, so long as the use expiry date is respected.

The invention therefore concerns an electrochemical sensor, being used to measure the concentration of a constituent in a solution, in the form of a tongue of small dimensions comprising a thin elongated insulating substrate supporting on either side of its median line two conductive strips of width L and L', whose facing edges are electrically insulated from each other by a space of width δ, widths L and L' and δ being measured perpendicularly to the median line, said substrate and said conductive strips being covered by a insulating covering film, into which are cut at one end a connecting window, and close to the other end, at least one measurement window formed of two openings separated by a portion of said covering film, each opening delimiting on a portion of each conductive strip the useful surfaces of a measurement electrode and of a reference electrode, characterised in that each opening has at any point dimensions, measured perpendicularly to the median line, such that the furthest edge from the edge of the portion of the strip forming the electrode which said opening does not uncover is situated at a distance comprised between L + δ and δ (respectively L' + δ and δ) and the closest edge at a distance greater than δ.

According to a preferred embodiment, in particular taking account of mass production in batches, the electrochemical sensor has an axial symmetry along its median line. The current collectors thus have the same width and the useful surfaces of the electrodes are identical.

Although the openings of the measurement windows may have any shape, a simple geometrical shape will be preferred, in particular because of the limitations of mass production and the search for minimum production cost. According to a preferred embodiment, each opening has the shape of a circular sector having the same surface and the portion of covering film intended to separate the openings has the shape of a narrow strip parallel to the conductive strips, having a width greater than δ, each of its edges covering a narrow portion of the two conductive strips.

The connecting and measurement windows may be cut into the covering film according to known techniques, but according to a preferred embodiment, such windows are cut by stamping said film. Tests carried out showed that stamping was the technique which allowed the most perfect reproducibility and thus the greatest precision to be obtained in the useful surfaces of the electrodes, whatever the manufacturing batch.

In a preferred application, the electrochemical sensor according to the invention allows the dosage of a constituent in a solution by further comprising on the measurement electrode a reactant containing at least one specific enzyme of the constituent whose concentration one wishes to measure and a chemical mediator allowing the electrons to be transferred.

As mediator, one of those described in US patent No 5 393 903 may be selected, namely mono, bis or tris 2,2' - substituted bipyridine complexes of ruthenium, osmium or vanadium, having at least one of the bipyridine ligands substituted by at least one electron donor group. Such mediators have the requisite properties as regards stability and mediation speed while not having any, or very little, influence on the deviation of a measurement as a function of the manufacturing batch of the sensor used.

In the application selected by way of example, namely the dosage of glucose in a patient's blood, the specific enzyme incorporated in the reactant will thus be glucose oxydase (GOD).

Other features and advantages of the invention will appear more clearly upon reading the detailed description which follows, concerning, by way of illustrative and non-limiting example, an electrochemical sensor comprising only one measurement window, such description being made with reference to the attached drawings in which:

- Figure 1 shows an enlarged top view of a sensor according to the invention, and

- Figure 2 shows the sensor of figure 1 along cross-section line II-II, on an even larger scale, the transverse dimensions having been exaggerated for better understanding.

Of course, the figures show the sensor in its ready to use form, i.e. after being cut out from its manufacturing batch, which may be either a strip or a sheet.

Referring to figures 1 and 2, there is shown a sensor for measuring the levels of glucose in the blood, i.e. an electrochemical sensor also comprising a reactant 18 the nature of which will be specified hereinafter. Such sensor has the shape of a thin tongue of small dimensions of a total thickness of between 0.25 and 0.75 mm, preferably approximately 0.5 mm; the width is between 6 and 12 mm, preferably approximately 8 mm; in the example selected comprising only one measurement window 11, its length is of the order of 40 mm.

Referring more particularly to the cross-section of figure 2, the sensor comprises a thin insulating substrate 1, made of a flexible but rigid material known to the man skilled in the art, such as PET.

Substrate 1 supports two conductive strips 4, 5 whose facing edges (4a, 5a) are electrically insulated by a space of width δ. In the example shown, these strips 4, 5

are substantially of the same width L = L'. It has been noted that, whatever the quality of the conductive material used, and even in the case of a metal plated conductive material, there may exist slight local variations of width which result, in sensors of the prior art, in which the conductive strips pass through the measurement window, in significant variations in the useful surface of the electrodes, the consequence of which is a lack of reproducibility in the measurement. When the two conductive strips 4, 5 are formed by a metal plated insulating film, they are laminated onto substrate 1 in a symmetrical manner, parallel to the median line of the sensor, leaving between them a narrow insulating space 6 having the shape of a strip of width δ.

The assembly thus formed by substrate 1 and conductive strips 4, 5 is covered by a thin insulating covering film 2 in which two windows 8 and 11 are cut, close to each end. Window 8 is a connecting window allowing portions of conductive strips 4, 5 to appear, said strips forming contacts 9, 10 which will allow the sensor to be connected to a portable electronic apparatus. As is seen in figure 1, the conductive strip portions pass across window 8 and allow a small strip of substrate 1 to appear close to their external ends. Window 11 is a measurement window having two openings 12, 13 which are symmetrical with respect to axis 3 of the sensor, and separated by a narrow portion 14 of the strip-shaped covering film. Openings 12 ,13 delimit on portions of conductive strips 4, 5 the surface of each electrode 16, 17, the dimensions of each opening 12, 13 being such that no portion of substrate 1 appears. For this purpose, for opening 12, its edge 12b furthest from edge 5a of the portion of strip 5 forming electrode 17 which said opening 12 does not uncover is at a distance d1 such that $1 + \delta > d1 > \delta$ and its closest edge 12a from said edge 5a is situated at a distance d2 such that $d2 > \delta$. Likewise, edge 13b of opening 13 is at a distance d'1 from edge 4a of the

portion of strip 4 forming electrode 16 which said opening 13 does not uncover such that $L' + \delta > d'1 > \delta$, and closest edge 13a is at a distance d'2 such that $d'2 > \delta$. All of distances d1, d2, d'1 and d'2, are measured perpendicularly to median line 3.

In the symmetrical configuration shown, $L = L'$, $d1 = d'1$ and $d2 = d'2$ and the openings have the shape of circular sectors separated by a strip 14 of width greater than δ, which covers facing edges 4a, 5a of the two portions of strips 4, 5 forming electrodes 16, 17, on a width substantially equal to the width of covering close to the furthest edges of each opening. Given the small dimensions of the sensor, this covering will be for example at the minimum of the order of 0.10 mm over all the periphery of each opening. As is seen, the surface of each electrode is very precisely delimited by the surface of each opening, by eliminating any surface variation due, either to irregularity of the edges of the conductive strips, or to small positioning variations of covering film 2 on substrate 1. Experience has shown that the greatest reproducibility in the surface of the openings is obtained by stamping film 2. The substrate and the covering film are kept attached to each other by known methods such as thermofusion of the facing surfaces, or application of an adhesive material.

There is also shown in figure 2 reactant 18 which covers the entire useful surface of measurement electrode 16.

In the case of glucose dosage, such reactant will be, for example, that described in US patent 5 378 628 giving optimisation conditions of a mixture comprising in particular glucose oxydase (GOD) and a mediator selected from the mono, bis or tris 2,2' - substituted bipyridine complexes of ruthenium, osmium or vanadium having a bipyridine ligand substituted by at least one electron donor group. Such reactant which allows, in particular measurement to be carried out in optimum conditions in

order to have a high diffusion speed which renders the response variations of the sensor as a function of the manufacturing batch of the reactant, or variations in quantity deposited on the measurement electrode, negligible or zero.

The invention thus provides a sensor which may thus be presented to the user in packaging comprising no calibrating means. The packaging may at the most comprise an expiry date for use, as is common for consumer products, in particular in the pharmaceutical field.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Electrochemical sensor, being used to measure the concentration of a constituent in a solution, in the form of a tongue of small dimensions comprising a thin elongated insulating substrate (1) supporting on either side of its median line (3) two conductive strips (4, 5) of width L and L', whose facing edges (4a, 5a) are electrically insulated from each other by a space (6) of width δ, widths L and L' and δ being measured perpendicularly to the median line (3), said substrate (1) and said conductive strips (4, 5) being covered by a insulating covering film (2), in which are cut out at one end a connecting window (8), and close to the other end, at least one measurement window (11) formed of two openings (12, 13) separated by a portion (14) of said covering film (2), each opening delimiting on a portion of each conductive strip (4, 5) the useful surfaces of a measurement electrode (16) and of a reference electrode (17), characterised in that each opening (12, 13) has at any point dimensions, measured perpendicularly to the median line (3), such that the furthest edge (12b, 13b) from the edge (4a, 5a) of the portion of the strip (4, 5) forming the electrode (17, 16) which said opening (12, 13) does not uncover is situated at a distance comprised between L + δ and δ (respectively L' + δ and δ) and the closest edge (12a, 13a) at a distance greater than δ.

2. Electrochemical sensor according to claim 1, characterised in that it has an axial symmetry with respect to its median line (3), the conductive strips (4, 5) having thus along their entire length substantially the same width L = L', and the useful surfaces of the electrodes (16, 17) being thus identical.

3. Electrochemical sensor according to claim 2, characterised in that each opening (12, 13) has the shape of a circular sector and that the portion (14) separating

the two openings has the shape of a strip parallel to the conductive strips (4, 5).

4. Electrochemical sensor according to claim 1, characterised in that the windows (8, 11) are made by stamping the covering film (2).

5. Electrochemical sensor according to claim 1, characterised in that the measurement electrode (16) is also covered with a reactant (18) containing at least one specific enzyme of the constituent present in the solution and a chemical mediator capable of transferring the electrons.

6. Electrochemical sensor according to claim 5, characterised in that the mediator is selected amongst the mono, bis or tris 2,2' - substituted bipyridine complexes of ruthenium, osmium or vanadium, at least one of the bipyridine ligands being substituted by at least one electron donor group.

7. Electrochemical sensor according to claims 5 or 6, characterised in that the enzyme is glucose oxydase (GOD) for effecting the glucose dosage.

8. Electrochemical sensor substantially as hereinbefore described with reference to the accompanying drawings incorporating any one or more of the novel features herein disclosed.

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 10186/97

Fig .1

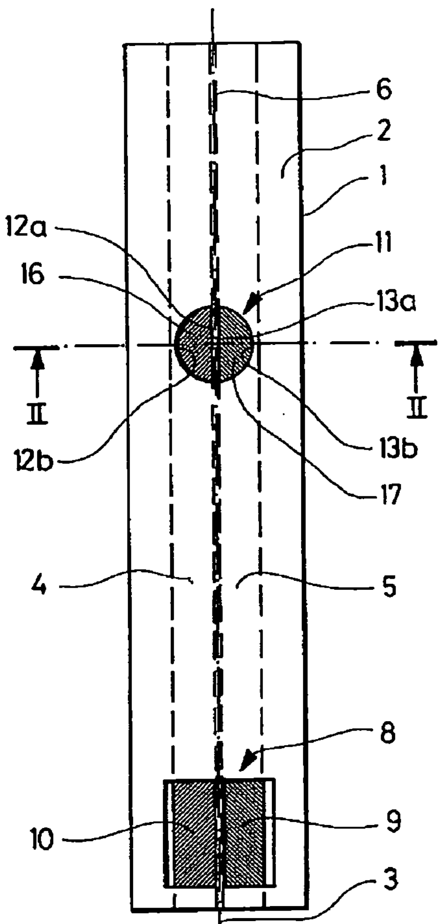

Fig . 2